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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,586	01/05/2004	Sergey M. Dzekunov	MAXC:013USD1	3107

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EXAMINER	
KETTER, JAMES S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,586	DZEKUNOV ET AL.	
	Examiner	Art Unit	
	James S. Ketter	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-129* is/are rejected.

7)☒ Claim(s) *102, 103, 116 and 124* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: _____.

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). Applicant Must Provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

At page 69 of the specification there are 2 oligonucleotide sequences which require compliance with 37 C.F.R. 1.821-1.825.

Please see the attached Notice to Comply.

Claims 122 and 123 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Both claims depend from claim 119, which is limited to erythropoietin or fragments thereof. However, the instant claims are drawn to IL12 or IL2, which are outside the scope of claim 119.

Claims 102, 103, 116 and 124 are objected to because of the following informalities:

Claims 102 and 103 have misspelled "are" as "art". Claim 116 mixes commas and semicolons in the listing of therapeutic agents. Also, claim 116 recites "agent" (singular) but lists many of such agents in the plural. Claim 124 misspells "field" as "filed". Appropriate correction is required.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-21, 43-87 and 127-129 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Application Serial No. 10/080,272, as follows: instant claims 1-14, 43, 44, 47-57, 60-67 and 127-129 over copending claim 1; instant claims 15, 16 and 78 over copending claim 12; instant claims 17-19

and 79 over copending claim 13; instant claims 20, 58 and 80 over copending claim 14; instant claims 21, 46, 59 and 82 over copending claim 16; instant claims 45 and 81 over copending claim 15; instant claims 68-77 and 83-87 over copending claims 2-11 and 17-21, respectively. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to all that is recited in the respective claims of the patent, i.e., the copending claims fall entirely within the scope of each of the respective instant claims, with the exception of instant claims 127-129. With respect to 127-129, the MPEP states, at §804, that

> [t]he specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Each of instant claims 127-129 is more narrowly drawn than the copending claim, merely by virtue of the instant claims specifying a spacing between the electrodes. However, the portion

of the copending application that supports each of the instant claims defines the copending invention including embodiments with the recited spacings. Thus, the method of the instant claims is not patentably distinct from that of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 48, 50-55, 62-66 and 124-129 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48, 50-55, 62-66, 126, 125, 126, 61, 61 and 61, respectively, of U.S. Application Serial No.10/225,446. Although the conflicting claims are not identical, they are not patentably distinct from each other because an obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). The MPEP states, at §804, that

> [t]he specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

The instant claim in each instance is more narrowly drawn than the copending claim, merely by virtue of the instant claims having "cm" recited where no units are recited in each of the corresponding copending claims. However, the portion of the copending application that supports each of the instant claims defines the copending invention in centimeters. Thus, the method of the instant claims is not patentably distinct from that of the copending claims. With respect to claim 126, the limitation to CLL-B cells is found in the copending specification as defining the invention of copending claim 126, and hence would have been an obvious limitation to the instant claim 126. Instant claims 127-129 are limited to spacings which are set forth in the copending specification in defining the invention of the copending claims, which therefore would have been obvious variants over the invention of the copending claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-47, 49, 56-61 and 67-116 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-47, 49, 56-61 and 67-116 of copending Application No. 10/225,446.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 50-55, 124, 125 and 127-129 are rejected under 35 U.S.C. 102(b) as being anticipated by Meserol (A57, of record on the IDS filed 30 May 2003).

Instant claims 50-55 are drawn to a flow electroporation device comprising a flow chamber with oppositely chargeable electrodes, wherein the surface area of the electrodes has a recited ratio over the spacing of the electrodes. However, as indicated in the rejection under 35 USC ə 112, second paragraph, below, this ratio is of a linear dimension over a linear dimension squared, which, in the absence of specified units of measure, is meaningless, as different length units will produce different ratios for the same chamber. Thus, the ratio limitation can be met for essentially any chamber having the other recited limitations, by merely selecting an arbitrary unit of length with which to measure. Claims 124 and 125 are drawn to a method of flowing particles to be electroporated through a flow channel and applying an electric field of greater than 0.5kV/cm, more narrowly claimed in Claim 125 as greater than approximately 3.5 kV/cm. Claims 127-129 are drawn to a flow electroporation device wherein the electrodes define a first and second wall of a flow channel, and wherein there is an inlet and an outlet flow portal, and

wherein the electrodes have a spacing of greater than 3 mm, more narrowly recited in claims 128 and 129 as approximately 4 mm to 2 cm, and approximately 5 mm to 1 cm, respectively.

Meserol teaches, e.g., at the Abstract, a flow electroporation system, with the chamber being exemplified in Figure 10 as having opposed electrodes. At column 15, first full paragraph, a field strength of approximately 3.2 kV/cm is taught, which meets the recited limitation of approximately 3.5 kV/cm. At the paragraph bridging columns 14 and 15, a spacing of 7 mm is taught.

Claims 50-55, 124 and 125 are rejected under 35 U.S.C. 102(b) as being anticipated by Hofmann et al. (A56, of record on the IDS filed 30 May 2003).

Instant claims 50-55 are drawn to a flow electroporation device comprising a flow chamber with oppositely chargeable electrodes, wherein the surface area of the electrodes has a recited ratio over the spacing of the electrodes. However, as indicated in the rejection under 35 USC э 112, second paragraph, below, this ratio is of a linear dimension over a linear dimension squared, which, in the absence of specified units of measure, is meaningless, as different length units will produce different ratios for the same chamber. Thus, the ratio limitation can be met for essentially any chamber having the other recited limitations, by merely selecting an arbitrary unit of length with which to measure. Claims 124 and 125 are drawn to a method of flowing particles to be electroporated through a flow channel and applying an electric field of greater than 0.5kV/cm, more narrowly claimed in Claim 125 as greater than approximately 3.5 kV/cm.

Hofmann et al. teaches, e.g., at the Abstract, a flow electroporation system, with the chamber being exemplified in Figure 3 as having opposed electrodes. At column 5, fourth full paragraph, a field strength of 20 kV/cm is taught.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 117-123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the rejection:

The nature of the invention. The claimed invention encompasses a gene therapy method, and as such, the method must be therapeutically useable to be enabled.

The amount of direction or guidance presented in the specification, and the presence or absence of working examples.

The specification as filed teaches no actual showing of successful treatment of a defect employing gene therapy techniques. No discussion of what levels of expression of any particular proteins would be required to treat a disease using gene therapy is offered. Furthermore, no teachings with respect to the number of cells to be implanted or amount of nucleic acid to be administered, for any particular disease condition, nor teachings with respect to the location of

such implantation or administration or other factors relating to the surgical aspects of the invention, nor even teachings with respect to the use of any particular expressed protein for any particular disease state, are set forth. These factors would have to be determined by trial-and-error methodology.

The state of the prior art, and the predictability or unpredictability of the art. Generally, the prior art had seen no successes in treatment methods of either the in vivo or the ex vivo type of gene therapy. Several reviews of the art are discussed below, which show that the problems of vector selection and, more importantly, persistence of predictable and useable levels of expression of the therapeutic protein, represented technical barriers to the practice of gene therapy methods. Verma et al. (U, cited in parent application) teaches, e.g., at the four paragraphs at page 240, starting with the paragraph bridging the left-hand and center columns, and ending with the second full paragraph at the right-hand column, that persistence of expression and adequate expression systems, i.e., enhancer-promoter combinations, were problematic in ex vivo gene therapy methods tried through that time. Furthermore, Table 2, at page 242, shows that none of the transfection systems extant at the time were suitable for actual treatment methods. Anderson (V, cited in parent application) sets forth the state of the art as of 1998. Specifically, Anderson makes clear that methods extant in the art, particularly vector selection, delivery methods and persistence of gene expression, were still inadequate to permit routine practice of the gene therapy, let alone any demonstrably successful practice at all. Both the first paragraph, left-hand column, at page 25 and the conclusory paragraphs at page 30 make clear that Anderson did not regard practice of gene therapy methods at all routine as of 1998. More recently, Juengst (W, cited in parent application) has taught that the actual outcome of a

gene therapy method is much less predictable than previously hoped, due to pleiotropic effects, and that only a few apparent successes have been seen, with 2 of 9 of which patients later developing T-cell acute lymphoblastic leukemia as a result of the inserted genetic material altering expression of a particular gene, LMO-2. Thus, it is clear that as of the filing date of the instant invention, gene therapy was regarded as essentially without successes and unpredictable

The quantity of experimentation. It is clear from the art, as shown by Verma et al., Anderson or Juengst, cited above, that a very large amount of experimentation had already been underway in the art as of 1997, 1998 and even 2003. Even with that amount of work, no successful gene therapy methods had been demonstrated. The references acknowledge the need for more work as of those dates. See, e.g., Verma et al. at page 239, at the first two introductory paragraphs; Anderson, e.g., at page 25, also at the first two introductory paragraphs, and the last two paragraphs at page 30; and Juengst at the first three paragraphs.

The breadth of the claims. The instant claims are drawn to the potential treatment of a wide variety of disease states, using a wide variety of cell types, and to a wide variety of proteins to be expressed in such treatment. As such, the claims would have been regarded by one of skill as very broad.

Conclusion. Were the skilled practitioner to have attempted to practice the claimed gene therapy methods, said practitioner first would have turned first to the specification for guidance in selecting dosages, treatment regimens and other factors which may bear upon the success of such treatment. However, as set forth above, such guidance in the specification is very limited in nature, and is insufficient with respect to prediction of proper levels of expression. Said practitioner then would have turned to the prior art to obtain detailed guidance for practice of the

claimed methods. However, as set forth above, the prior art does not recognize any clearly successful gene therapy methods. Instead, the high degree of unpredictability of the art is taught, especially in the latest cited reference, Juengst. Thus, the skilled practitioner would not have been able to find the necessary guidance in the prior art. Finally, said practitioner would have been forced to turn to empirical experimentation to determine appropriate dosages, treatment regimens and other factors, required for successful practice of a gene therapy method. However, as set forth above, the amount of experimentation recognized by the art as required for development of a successful gene therapy protocol is very large, and of a largely trial-and-error nature. Furthermore, as set forth above, the field of gene therapy is unpredictable. A large amount of experimentation in an unpredictable art with little or no available guidance is clearly undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50-55, 62-66, 104 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50-55 and 62-65 recite a limitation to the ratio of electrode surface area to electrode spacing. However, as set forth in the rejections under 35 USC § 102(b), above, this ratio is of a linear dimension over a linear dimension squared, which, in the absence of specified units of measure, is meaningless, as different length units will produce different ratios for the

same chamber. For example, if the surface area were 100 mm^2, and the spacing were 10 mm, the ratio would be 10. However, if the same device were measured in cm, the ratio would be 1 cm^2 over 1 cm, or 1. Thus, the ratio limitation can be met for essentially any chamber having the other recited limitations, by merely selecting an arbitrary unit of length with which to measure. As such, it is not clear how this limitation sets the metes and bounds of the instant claims.

Claim 66 recites "not substantially thermally degraded". However, it is not clear what degree of degradation is encompassed by this limitation. As such, the metes and bounds of the claim are not clear.

Claims 104 and 118 both end with "VEGF, or soluble growth factor and any fragments or combinations thereof." However, as such, the "and" would cause the claim to encompass only combinations of one of the recited members of the list before the "and" with "any fragment" or "any combination" of said members. Thus, either a combination of one of said members with a fragment of one of said members is encompassed, or a combination of one of said members with a further combination of two of said members, i.e., a combination of three of said members, is encompassed, but nothing else. Applicants should consider using a proper Markush-type group to clarify the instant claims.

Any inquiry concerning this communication or earlier communications from the Examiner with respect to the examination on the merits should be directed to James Ketter whose telephone number is (571) 272-0770. The Examiner normally can be reached on M-F (9:00-6:30), with alternate Fridays off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Remy Yucel, can be reached at (571) 272-0781.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Jsk
July 6, 2005

JAMES KETTER
PRIMARY EXAMINER